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Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial

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Summary

Background Observational studies have postulated a therapeutic role of metformin in treating COVID-19. We conducted an adaptive platform clinical trial to determine whether metformin is an effective treatment for high-risk patients with early COVID-19 in an outpatient setting.

Methods The TOGETHER Trial is a placebo-controlled, randomized, platform clinical trial conducted in Brazil. Eligible participants were symptomatic adults with a positive antigen test for SARS-CoV-2. We enrolled eligible patients over the age of 50 years or with a known risk factor for disease severity. Patients were randomly assigned to receive either placebo or metformin (750 mg twice daily for 10 days or placebo, twice daily for 10 days). The primary outcome was hospitalization defined as either retention in a COVID-19 emergency setting for > 6 h or transfer to tertiary hospital due to COVID-19 at 28 days post randomization. Secondary outcomes included viral clearance at day 7, time to hospitalization, mortality, and adverse drug reactions. We used a Bayesian framework to determine probability of success of the intervention compared to placebo.

Findings The TOGETHER Trial was initiated June 2, 2020. We randomized patients to metformin starting January 15, 2021. On April 3, 2021, the Data and Safety Monitoring Committee recommended stopping enrollment into the metformin arm due to futility. We recruited 418 participants, 215 were randomized to the metformin arm and 203 to the placebo arm. More than half of participants (56.0%) were over the age of 50 years and 57.2% were female. Median age was 52 years. The proportion of patients with the primary outcome at 28 days was not different between the metformin and placebo group (relative risk [RR] 1.14[95% Credible Interval 0.73; 1.81]), probability of superiority 0.28. We found no significant differences between the metformin and placebo group on viral clearance through to day 7 (Odds ratio [OR], 0.99, 95% Confidence Intervals 0.88–1.11) or other secondary outcomes.

Interpretation In this randomized trial, metformin did not provide any clinical benefit to ambulatory patients with COVID-19 compared to placebo, with respect to reducing the need for retention in an emergency setting or

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hospitalization due to worsening COVID-19. There were also no differences between metformin and placebo observed for other secondary clinical outcomes.

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Research in context

Evidence before this study

A search of PubMed on Sept 10, 2021 by means of the following search terms “(randomized OR trial) AND (metformin) AND (COVID* OR SARS-CoV-2 OR SARS-CoV)”, with no date or language restrictions. We identified one observational study that found lower mortality, but similar hospitalizations among patients receiving metformin (Ghany et al. 2021). Another study found a reduced risk mortality in women receiving metformin, but not men (Bramante et al. 2021) A third retrospective study found metformin use was associated with higher acidosis in patients with COVID-19 (Cheng et al. 2020).

Added value of this study

The TOGETHER Trial is the first randomized trial to date to assess the effectiveness of metformin for patients with COVID-19. Compared with placebo, patients randomly assigned to metformin had no significant benefit in reducing hospitalization, defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19.

Implications of all the available evidence

Results from this randomized clinical trial provide evidence that metformin does not show effect on reduced hospitalizations or mortality. These findings should guide subsequent COVID-19 clinical research.

Introduction

Metformin is the most prescribed type 2 diabetes medication due to its ability to lower blood glucose by suppressing hepatic glucose production. In addition to its ability to lower blood glucose, metformin decreases levels of TNF α , adipokines and IL-6, and increases levels of IL-10, which have been observed both in experimental studies and in studies carried out in patients with type 2 diabetes mellitus.^{1–3} The effects associated with the reduction in circulating adipokines may minimize the degree of inflammatory response and thus reduce the severity of the disease.⁴

Evidence from retrospective observational studies suggests metformin may be clinically beneficial for

patients with COVID-19. One observational study found lower mortality, but similar hospitalizations among patients receiving metformin. Another study found that metformin was significantly associated with reduced mortality in women with obesity or type 2 diabetes who were admitted to hospital for COVID-19.⁵ Another retrospective cohort study of hospitalized patients with COVID-19 found that those on metformin had significant increased incidence of acidosis, however, the study did not find a significant difference in 28-day COVID-19 mortality.⁶

Considering these potentially important findings are limited to observational evidence, there is a need for randomized trials to test the effectiveness of metformin in patients with COVID-19, particularly in outpatients where metformin use is common, however observational evidence is lacking. Treating COVID-19 early in outpatient settings may be key to preventing progression of the disease.⁷ To evaluate the effectiveness of a number of repurposed therapies in preventing hospitalization due to the progression of COVID-19, we conducted a randomized, placebo-controlled adaptive platform trial in Minas Gerais, Brazil (the TOGETHER Trial). Herein, we report on the clinical evaluation of metformin compared to placebo.

Methods

Study design

The TOGETHER Trial is a randomized adaptive platform trial to investigate the efficacy of repurposed therapies for COVID-19 disease among high-risk adult outpatients.⁸ The trial was designed and conducted in partnership with local public health authorities from ten participating cities in the Minas Gerais state of Brazil. The web-appendix lists all participating clinical sites and investigators.

The protocol for this trial began recruiting patients on June 2, 2020 and began enrolling into the metformin arm on January 15, 2021. This protocol was approved in compliance with the International Conference of Harmonization – Good Clinical Practices, as well as local regulatory requirements. The trial was approved for research ethics by local ethics board in Brazil (CAAE: 41,174,620.0.1001.5120) as well as the Hamilton Integrated Research Ethics Board (HiREB approval letter 13,390) in Canada. The master protocol,

statistical analysis plan, and additional study details can be found in the Open Science Framework (doi.org/10.17605/OSF.IO/EG37X). We used the adaptive designs CONSORT extension (ACE) statement for reporting this trial.⁹

Participants

We included participants who were at least 18 years or older, presented to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date, and who had a positive test using the Panbio[®] rapid antigen test for SARS-CoV-2. Eligible participation also required at least one additional criterion for high-risk: diabetes mellitus; systemic arterial hypertension requiring at least one oral medication for treatment; known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion); symptomatic lung disease and/or being treated (emphysema, fibrosing diseases); symptomatic asthma patients requiring chronic use of agents to control symptoms; smoking; obesity, defined as BMI > 30 kg/m² (weight and height information provided by the patient); transplant patients; patient with stage IV chronic kidney disease or on dialysis; immunosuppressed patients/using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy; patients with a history of cancer in the last 5 years or undergoing current cancer treatment. Patients (age ≥ 50 years) did not need any other risk criteria.

Inclusion and Exclusion Criteria

Patients who met any of the following criteria were excluded from the study: (1) Diagnostic examination for SARS-CoV2 negative associated with acute flu-like symptoms (patient with negative test taken early and becoming positive a few days later is eligible, if he/she is < 7 days after the onset of flu-like symptoms); (2) Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need; (3) Patients with acute respiratory condition due to other causes; (4) Patients who have received vaccination for SARS-CoV2; (5) Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension). A full list of exclusion criteria can be found in the trial protocol.

Randomization and masking

We randomized patients to the metformin and placebo arms stratified to account for other arms in the trial. Randomization was also stratified by clinical site and

age (≥ 50 years vs < 50 years). Patients, investigators, health-care providers and sponsors were masked to the study drug assignment. The randomization schedule was prepared by the study pharmacist and provided to blinded site staff. Randomization lists were prepared and kept confidential by an unblinded statistician and treatment packages were prepared by an unblinded pharmacist. With each newly eligible participant, the clinician contacted the unblinded pharmacist by WhatsApp to request a code that corresponded to a blinded treatment package.

Patients assigned to the metformin arm received a 750 mg dose twice daily for a period of 10 days. The dose of metformin was selected based on prior observational evidence of a dose response greater than 1000 mg daily and aligned with the dose used in a similar outpatient trial currently recruiting (NCT04510194). Patients assigned to the placebo arm received corresponding tablets of inert material (talc). Placebo tablets were matched for the same number of tablets as active metformin (10). As this is a multi-arm trial, all active interventions had a matching number of days of placebo, proportionate to the number of active arms in the trial at any given time. For example, if there were two active arms in a trial, then the placebo allocation to matched placebo was 2:2.

Procedures

The trial consisted of a face-to-face screening visit (day 0) and follow-up visits completed through telephone contact and WhatsApp using video-teleconferencing. At baseline, cardiac safety was assessed using a 6-lead ECG (Kardiamobile, Mountain View, CA). The digital recordings were de-identified and transferred to a central facility (Cardresearch, Belo Horizonte, Brazil) for reading. Oxygen status was assessed using a pulse oximeter for non-invasive arterial oxygen saturation (SpO₂) and pulse (Jumper Medical Equipment, Shenzhen, China), and temperature using a standard digital oral thermometer. Follow-up visits were performed on days 1–5, 7, 10, 14, and 28. Participants were also contacted on day 60 post-randomization, to assess longer-term outcomes. Patients were contacted during the study drug period for adherence, adverse drug reactions, adverse events, assessment of the WHO clinical worsening scale, any hospitalization or retention in an COVID-19 emergency setting, concomitant medications information, and PROMIS Global Physical Health Scale (day 14, 28 and 60). Unscheduled visits (during the treatment period) occurred at any time in case of adverse events. Mid-turbinate nasal swab kits and sterile recipient storage were provided for collection of nasopharyngeal swab or sputum/saliva. These procedures for PCR testing were performed on the first quarter of participants enrolled in the trial on days 3 and 7.

Outcomes

The primary outcome was hospitalization defined as retention in a COVID-19 emergency setting visits with participants remaining under observation for more than 6 h or referral to tertiary hospital care for COVID-19, within 28 days of randomization. This region of Brazil implemented hospital-like services in the emergency setting with 50–80 beds that provided services including oxygenation, sedation, multi-day stays, and mechanical ventilation. Primary clinical events were adjudicated by an independent event adjudication committee that did not consider patient wait times as contributing to the 6 h threshold for emergency room stays.

Secondary outcomes were WHO clinical worsening scale, PROMIS Global Physical or Mental Health Scale, all-cause mortality, viral clearance at days 3 and 7, adverse events and adverse drug reactions, and study adherence. All serious and non-serious adverse events were reported as per local regulatory requirements. Reportable adverse events included serious AEs (SAE), AEs resulting in study medication discontinuation, and AEs assessed related to study medication.

Statistical analyses

Our study is adaptive and applies sample size re-estimation approaches. To plan for each arm, we assume minimum clinical utility of 37.5% (relative risk reduction) to achieve 80% power with 0.05 two-sided Type I error for a pairwise comparison against the placebo (talc) assuming a control event rate (CER) of 15%. This results in an initial plan to recruit 681 participants per arm. Planned interim analyses were conducted. Stopping thresholds for futility were established if the posterior probability of superiority was less than 40% for ITT at the second interim analysis. An arm can be stopped for superiority if the posterior probability of superiority meets the threshold of 97.6%.

Baseline characteristics are reported as proportions or median and IQR for continuous variables. We applied a Bayesian framework for our primary analysis and a frequentist approach for all sensitivity analyses and secondary outcomes. Posterior efficacy of metformin vs. placebo for the primary outcome was calculated using the beta-binomial model for event rates, assuming uniform priors for both Intention-to-Treat (ITT), modified ITT (defined as receiving the study drug for at least 24 h before an event) and Per-Protocol (PP) analyses (defined as taking >80% of possible doses). We accounted for any temporal changes in events rates by selecting placebo concurrent with metformin randomization.

For viral clearance we fitted a longitudinal, mixed-effect logistic regression model with a treatment and time interaction term for binary patient outcomes (COVID-19 positive/negative) reported on days 3 and 7 from randomization, with subject random effect. PP analyses were considered sensitivity analyses to assess

the robustness of the results. All analyses were performed using R version 4.0.3.

A Data and Safety Monitoring Committee provided independent oversight for this trial. We planned a second interim analysis of metformin vs. placebo after 50% of data collected. Herein, we present follow-up of all patients allocated to these arms up to April 03, 2021.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation or writing, or decision to submit for publication. The executive committee take responsibility for the integrity of the data and the accuracy of the data analysis. The trial executive committee oversaw all aspects of trial conduct, completeness, data accuracy and adherence of trial conduct to the protocol and the committee vouch for the accuracy and completeness of the data and for fidelity to the protocol.

Results

In total, 3159 were screened for inclusion in the TOGETHER as of April 3, 2021 and 418 patients were included in this analysis. The median age was 52 years (range 18–90) and 239 (57.2%) were women (Table 1). Most participants self-identified as mixed-race; 381 (91.1%), 8 (1.9%) as white, 6 (1.4%) as black or African, the rest self-identified as other or unknown 23 (5.5%). Of the total 418 patients in this study, 215 were allocated to the metformin arm, and 203 were allocated to the placebo arm (Fig. 1). With respect to patient characteristics of age, Body Mass Index (BMI), and co-morbidities, the groups were generally well balanced (Table 1).

Primary outcome

In the metformin group, 34 (13.0%) participants were hospitalized or retained in a COVID-19 emergency setting for greater six hours compared to 28 (15.1%) in the placebo group. Based on the Bayesian beta-binomial model, there was no evidence of an effect of metformin over placebo on the primary outcome of hospitalization, defined as either retention in a COVID-19 emergency setting for > 6 h or transfer to a tertiary hospital due to COVID-19 for either the ITT population (Relative Risk [RR]: 1.14; 95% Bayesian Credible Interval [BCI]: 0.73 to 1.81), the mITT population (RR: 1.03; 95% BCI: 0.64 to 1.66), or the PP population (RR: 0.88; 95% BCI: 0.45 to 1.71) (Table 2). The probability that the event rate was lower in the metformin group compared to placebo was 28.4% for the ITT population and 64.4% for the PP population (Fig. 2) (Table 2).

Secondary outcomes

Clinical improvement at day 28, defined as the time to reporting a score of 0 on the World Health Organization

	Metformin(n = 215)	Placebo(n = 203)	Total(n = 418)
Sex			
Female	119(55.3)	120(59.1)	239(57.2)
Male	96(44.7)	83(40.9)	179(42.8)
Race			
Mixed Race [*]	195(90.7)	186(91.6)	381(91.1)
White	5(2.3)	3(1.5)	8(1.9)
Black or African American	2(0.9)	4(2.0)	6(1.4)
Unknown	13(6.0)	10(4.9)	23(5.5)
Age, years			
≥ 50 years	114(53.0)	120(59.1)	234(56.0)
Age Descriptive Statistics			
Median	52 (18–89)	52 (18–90)	52 (18–90)
IQR	18	17	17
Body Mass Index (BMI)			
<30 kg/m ²	121(56.3)	108(53.2)	229(54.8)
≥30 kg/m ²	94(43.7)	94(46.3)	188(45.0)
Unspecified	0(0.0)	1(0.5)	1(0.2)
Time since onset of symptoms			
0–3 days	100(46.5)	84(41.4)	184(44.0)
4–7 days	72(33.5)	77(37.9)	149(35.6)
Unspecified	43(20)	42(20.7)	85(20.3)
Risk factors			
Chronic cardiac disease	8(3.7)	6(3.0)	14(3.3)
Hypertension	88(40.9)	79(38.9)	167(40.0)
Chronic pulmonary disease	3(1.4)	2(1.0)	5(1.2)
Asthma	19(8.8)	15(7.4)	34(8.1)
Chronic kidney disease	1(0.5)	1(0.5)	2(0.5)
Rheumatologic disorder	2(0.9)	0(0.0)	2(0.5)
Diabetes mellitus: Type 1	5(2.3)	6(3.0)	11(2.6)
Diabetes mellitus: Type 2	31(14.4)	19(9.4)	50(12.0)
AIDS / HIV	0(0.0)	1(0.5)	1(0.2)
Autoimmune disease	2(0.9)	2(1.0)	4(1.0)
Smoking	11(5.1)	14(6.9)	25(6.0)
Any other co-morbidities or risk factor	25(11.6)	21(10.3)	46(11.0)

Table 1: Patient characteristics by treatment allocation in the TOGETHER Trial.

^{*} Self-identified as someone with mixed-race ancestry.

clinical worsening scale, was not different for patients allocated to metformin compared to placebo in the ITT population (Odds Ratio [OR]: 1.05; 95% CI: 0.71–1.56). With respect to the PROMIS, there was no significant difference observed for Global Physical Scale ($p = 0.63$).

In our mixed-effect logistic regression model, the clearance for the metformin (odds ratio [OR], 0.99; 95% Confidence Interval [95% CI]: 0.88–1.11) group did not differ in comparison with the control group (Supplementary Table 1) for the ITT population.

At 28 days of follow-up, there were 16 (3.8%) fatalities in total. Nine of these deaths were in the placebo arm (4.4%), while 7 (3.3%) were in the metformin arm ($p = 0.53$).

Treatment-emergent adverse events (TEAE) were categorized Grades 1–5 based on the severity of the

adverse event. There were 51 (23.7%) treatment-emergent adverse events in the metformin arm, of which 34 (15.8%) were serious and 1 (2.0%) led to discontinuation of the study drug. In the placebo arm, we recorded 47 treatment-emergent adverse events, of which 29 were serious (14.3%) with none lead to discontinuation. No significant differences across each grade of TEAE was observed, with the exception of there being less TEAEs in the placebo arm for Grade 3, indicating severe, or medically significant but not immediately life-threatening conditions, hospitalization or prolongation of hospitalization (Fig. 3).

With respect to adherence, at the time the recruitment of the metformin arm was stopped, 47 (21.9%) participants in the metformin group did not complete all phases of the study. Twenty-four (11.8%)

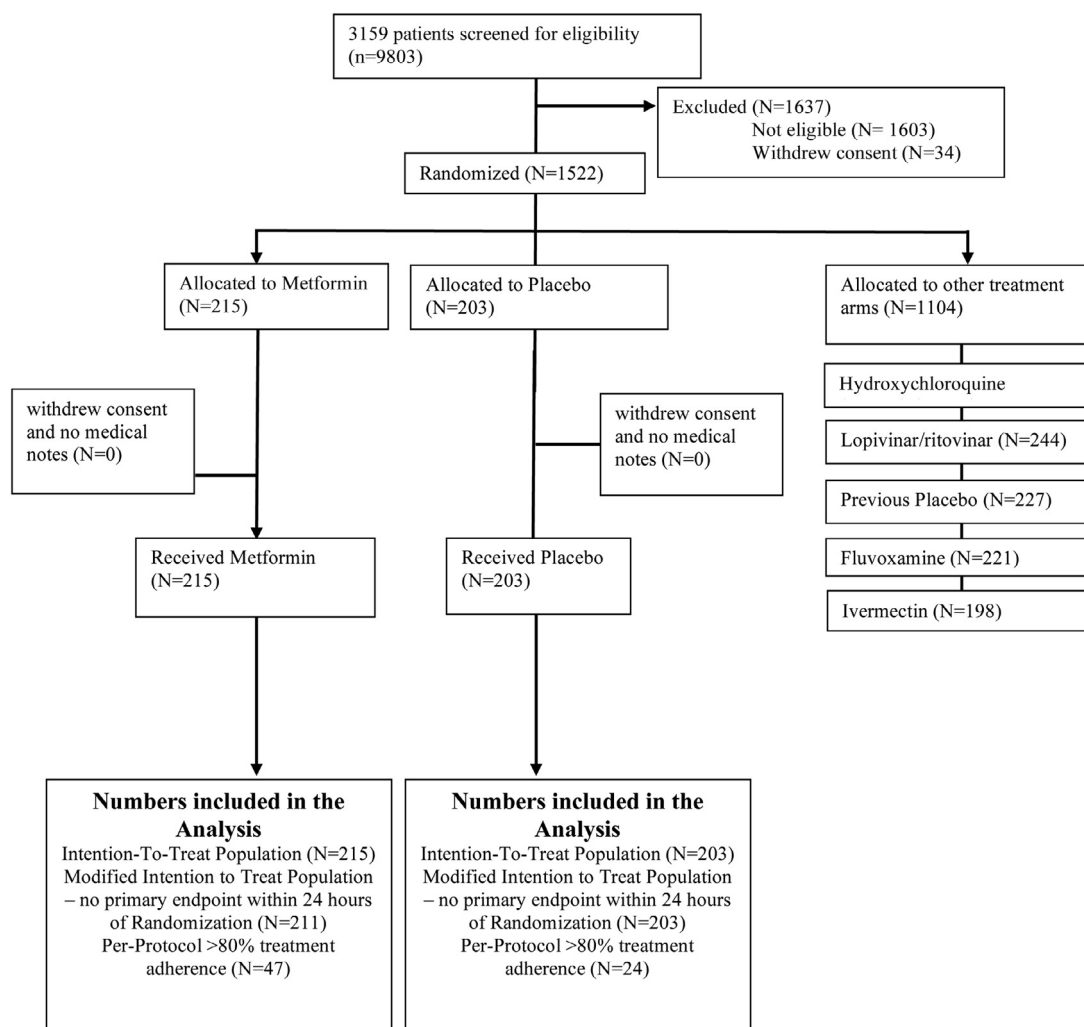


Fig. 1. Flow diagram of participants in the TOGETHER trial.

participants did not complete the study in the placebo group (Fig. 1).

Sub-group analyses

There were no significant differences observed across sub-groups of interest (web-appendix). For patients with diabetes, the odds of a primary outcome were 0.95 (95% CI: 0.51 – 1.78) favoring metformin.

Discussion

We found no significant effect of metformin vs. placebo as an early treatment in a community setting for COVID-19 in reducing hospitalizations, defined as retention in a COVID-19 emergency setting for > 6 h or transfer to a tertiary hospital for COVID-19. We similarly observed no benefit for the use of metformin on any measured secondary outcomes in our trial. The

TOGETHER Trial is continuing evaluations of other interventions for the early treatment of COVID-19.¹⁰

Our rationale for investigating metformin as a possible early treatment for COVID-19 came from pre-clinical and mixed observational evidence suggesting a possible role of metformin in reducing COVID-19 disease severity. Pre-clinical evidence has shown that metformin has immunomodulatory activity that reduces the production of proinflammatory cytokines using macrophages and causes the formation of neutrophil extracellular traps (NETs), as well as inhibiting cytokine production of pathogenic Th1 and Th17 cells, and may even directly inhibit SARS-CoV-2 replication.⁴ Observational and retrospective studies have also suggested that metformin may reduce in-hospital mortality and inflammatory burden among patients with COVID-19.

We observed a large difference between event rates in the ITT and PP populations. To explain this, we looked further into adherence by event category for both

Intention to treat (ITT)			
	N	n (%)	RR (95% BCI)
Metformin	215	34 (15.8)	1.14 (0.73 – 1.81)
Placebo	203	28 (13.8)	1.00 (Ref)
All	418	59 (14.8)	–
Modified Intention to Treat (mITT)			
	N	n (%)	RR (95% BCI)
Metformin	211	30 (14.2)	1.03 (0.64 – 1.66)
Placebo	203	28 (13.8)	1.00 (Ref)
All	414	58 (14.0)	–
Per Protocol (PP)			
	N	n (%)	RR (95% BCI)
Metformin	168	14 (8.3)	0.88 (0.45 – 1.71)
Placebo	179	17 (9.5)	1.00 (Ref)
All	347	31 (8.9)	–

Table 2: Proportion primary outcome.
RR = Relative Risk.
BCI = Bayesian Credible Interval.

placebo and metformin. Looking at adherence rate by event category, there was roughly a 35% reduction in adherence for those who required hospitalization or retention in a COVID-19 emergency setting among the placebo recipients, while adherence dropped by more than 50% in the metformin recipients with the same outcome. As the drop in adherence among those who had events occurred in both the placebo recipients and metformin recipients, this suggests that it is unlikely that reduced adherence leads to event, but rather those with severe disease were less adherent. In addition, metformin was compared to a common control for all arms, which also might explain the difference in adherence. The control used in the TOGETHER Trial was placebo dosed proportionate to the concurrent active treatment arms; for example, if the trial was randomizing to a 10-day intervention and a 3-day intervention, then half

placebo patients would receive a 3-day placebo while the other half received a 10-day placebo. This means that adherence is more likely in a 3-day placebo vs. a 10-day placebo.

One study found that metformin use was not associated with significantly decreased mortality among patients hospitalized with COVID-19, however it was associated with decreased mortality among women but not men.⁵ In another study among patients hospitalized with COVID-19 found that metformin use was significantly associated with higher incidence of acidosis and decreased heart failure and inflammation, but not 28-day mortality.⁶ The differences in the results of these studies and our clinical trial may be due to differences in dose-dependency and likely suggest that longer-term use of metformin may provide greater benefit than acute administration.

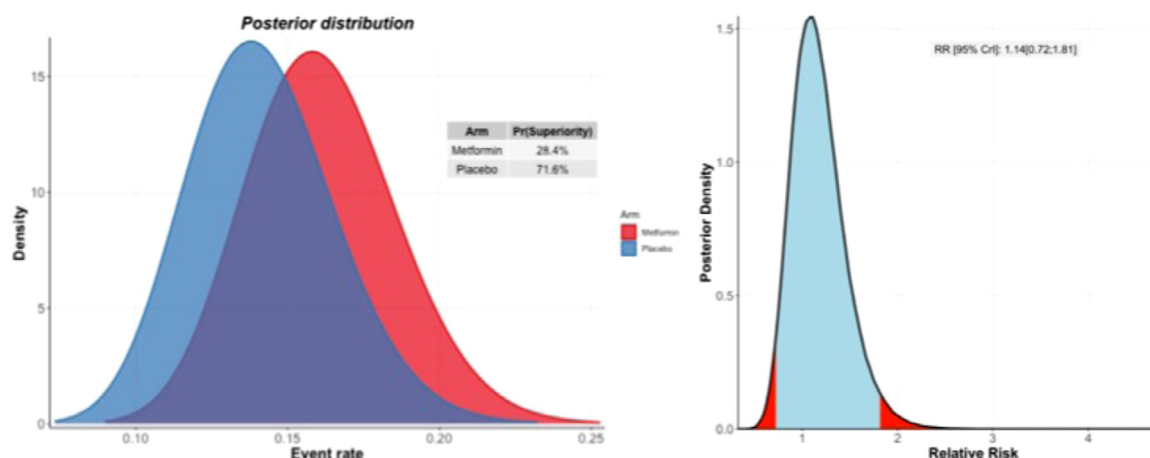


Fig. 2. Probability of efficacy and Bayesian relative risk. A: Intention-to-treat analysis; B: Per-protocol analysis.

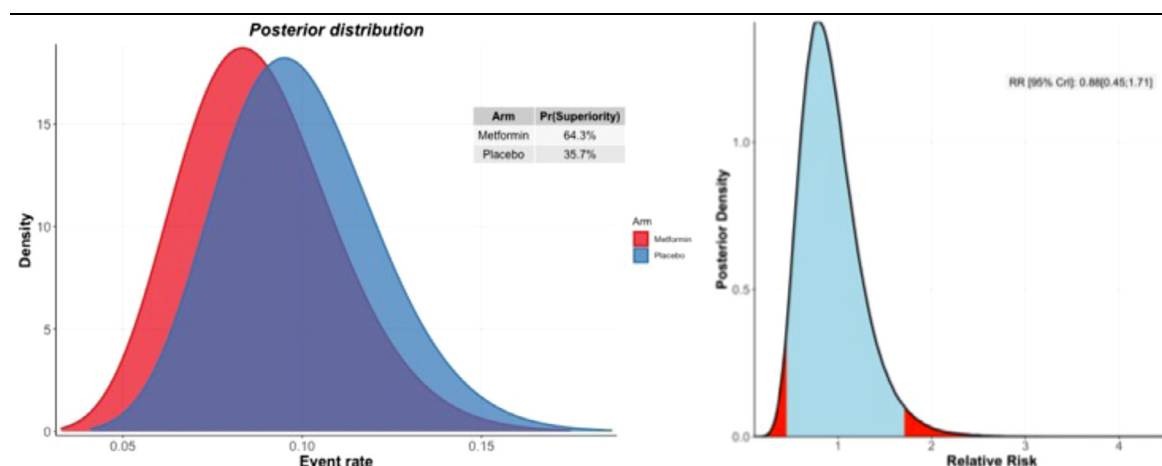


Fig. 2 Continued.

Our study is a platform adaptive design with multiple arms and the potential to add or drop arms for the purpose of efficiency.¹¹ Our DSMC has previously recommended stopping treatment arms for lack of benefit with hydroxychloroquine or lopinavir/ritonavir vs. placebo.¹⁰ Stopping treatment arms early for lack of treatment effect is an accepted strategy for reducing waste and, in the context of platform trials, allowing the trial to replace the treatment arms with next available interventions while maintaining the infrastructure of patient recruitment and staffing. Much has been reported about both the merits of interim evaluations and the potential for types 1 and 2 error, in particular for stopping trials

early for superiority.¹² In this case, our intervention arm was stopped early due to undetectable differences against placebo, and we have used this trial efficiency to replace the treatment arm with a new drug. The trial now continues to evaluate the effect of doxazosin and peginterferon lambda vs. placebo.

Since the pandemic first began, there have been more than 2800 RCTs registered on clinicaltrials.gov, yet less than 300 have been reported and the vast majority of clinical trials have been small, with sample sizes less than 100.¹³ In many cases, the trials have been unsuccessful at recruiting as the local epidemics have occurred in waves and most trials did not have

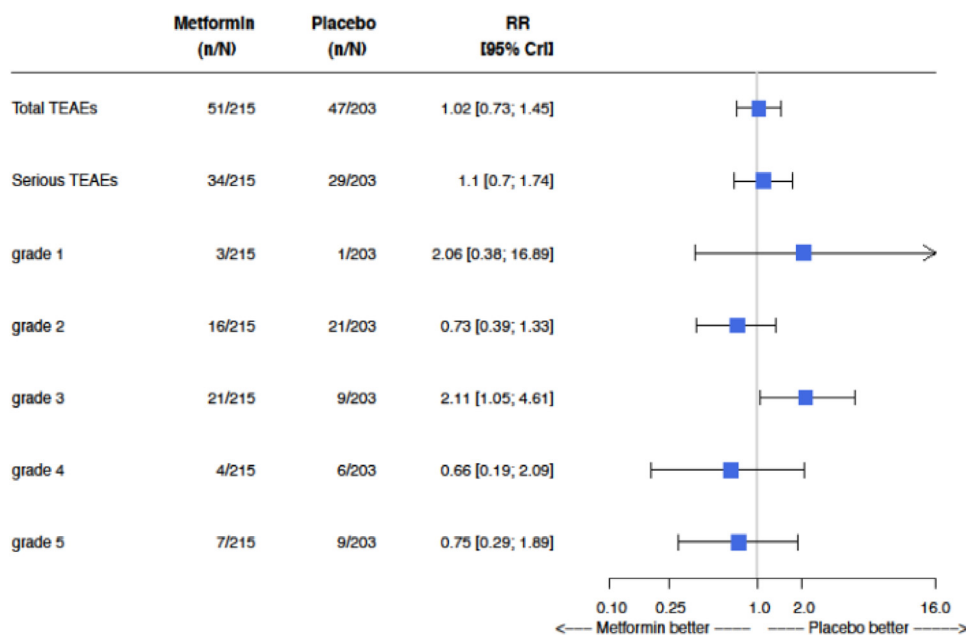


Fig. 3. Treatment-emergent adverse events in the TOGETHER Trial.

sustainable infrastructure to maintain staff or local interest for recruitment. The trials that have had the greatest contributions to our medical understanding tend to be the larger platform trials, such as SOLIDARITY, RECOVERY, PRINCIPLE, and REMAP-CAP. We actively collaborate with other investigators running trials with overlapping interventions so that they can be aware of our study decisions and determine whether they should influence their respective trials. The University of Minnesota study evaluating metformin among a matched population to ours is continuing recruitment (NCT04510194).

Our current study has both strengths and limitations. Strengths include the rapid recruitment and enrolment of patients at high-risk of developing severe COVID-19. Our recruitment strategy engaged with the local public health system, thus allowing recruitment that frequently exceeds twenty patients per day. Our understanding of the epidemiology of COVID-19 as well as the disease progression and outcomes of patient importance have evolved since beginning this trial in June 2020. We made adaptations to the trial according to prespecified rules and in communication with the appropriate ethics review committees that allowed us to respond to the epidemic waves while maintaining high rates of recruitment. Unlike many outpatient clinical trials, our study involves direct patient contact through the use of medical students, nurses and physicians who do at-home visits as well as follow-up via telecommunications. Given the rapid recruitment of patients as well as the high event rate of retention in COVID-19 emergency settings and hospitalizations due to worsening COVID-19, we were able to evaluate the effects of interventions when portions of the planned population had been recruited. The period of time between first recruitment of a patient on metformin and discontinuing the treatment arm for our trial was 78 days. The rapid discontinuation of this treatment arm increased allocation to other treatment arms as well as allowed us to enter a new intervention into the trial for evaluation.

Limitations of our trial primarily relate to the challenges of conducting a trial in a disease that is not well characterized. No standard of care exists for early treatment of COVID-19 and various advocacy groups promote different interventions, including some of those evaluated in our trial. We mitigated this by inquiring of any treatments a patient may have tried as per their own decision-making or that of a prescribing clinician. The medical/scientific community still does not understand who is at greatest risk of disease progression from this disease as some patients with numerous risk factors do recover quickly while some others with less established risk factors may not. The rate of our primary endpoint occurring appears to have increased importantly from the beginning of the trial to the end of the trial. This is likely explained by the emergence of the predominant Gamma (P.1) variant during the conduct of this

trial that may exhibit greater transmission and worse clinical outcomes than earlier variants. This is, as yet, still poorly understood.

In conclusion, several retrospective observational studies have suggested that metformin treatment may have potential benefit in patients with COVID-19. Repurposing existing drugs is an appealing strategy to respond to the pandemic. Our trial found no clinical benefit to support the use of metformin in an outpatient population. This adds to the evidence that metformin should not be specifically repurposed for the treatment of early COVID-19.

Contributors

EJM and GR decided to publish the paper. EJM, GR, EASMS, DCMS, LT, ACM, TSF, CVQS, EDC, ADFN, LCMS, MICS, LBR, RO, OH, JIF, HR, SS, PM, AVG, CRR, EL, AMR, and GG contributed to trial design. EJM, GR, JIF, EASMS, DCMS, LT, TSF, CVQS, ACM, EDC, ADFN, LCMS, MICS, LBR, RO, OH, JIF, HR, SS, PM, and CRR helped plan the trial and ongoing recruitment. GR, EJM, EASMS and DCMS were responsible for acquisition of data. EJM, GR, JIF, OH, HR, PM, AVG, SS, RO, CRR, LT and GG drafted the manuscript. OH, HR, and EJM contributed to the statistical analysis. All authors critically revised the manuscript. The members of the TOGETHER Trial Collaborative Group and their roles in the conduct of the trial are listed in the appendix. All authors had full access to all of the data in the study and take final responsibility for the decision to submit for publication. EJM and GR accessed and verified the underlying data.

Data sharing

Data from the TOGETHER trial will be made available following publication of this manuscript to interested investigators through the International COVID-19 Data Alliance after accreditation and approval by the TOGETHER trial principal investigators (EJM and GR). Other study related documents can be found in the Open Science Framework.

Registration

ClinicalTrials.gov: [NCT04727424](https://clinicaltrials.gov/ct2/show/study/NCT04727424).

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Declaration of Interests

EM, AG, SS, PM, and JF have been employed by Platform Life Sciences. EM, JF, OH, RH have been employed by Cytel. CR has been employed by Certara. GR has been employed by Cardresearch.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lana.2021.100142](https://doi.org/10.1016/j.lana.2021.100142).

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